

Epidemiology

The company does not accept there is credible evidence that glyphosate use can cause NHL.

The panel classified the epidemiological data as 'limited evidence' based on associations in some case-control studies (studies of volunteers where exposure data is collected after NHL has been diagnosed for cases, but without such a precipitating event for controls). Such studies are well known to be prone to a number of biases, especially enhanced recall of exposures by cases.

The IARC panel makes clear, in the largest and single most important study into the health of pesticide applicators (the Agricultural Health Study (AHS) or Ag Health Study), that there was no link with NHL (De Roos et al., 2005). The AHS is the largest cohort study conducted of approximately 60,000 licensed pesticide applicators that was set up in the 1990s to provide a large unbiased set of data to examine cancer and other health risks in pesticide applicators. In the Ag Health Study, information on pesticide use was collected before follow-up for cancer and other outcomes. In this study, there was no greater risk of NHL in all applicators when their cancer experience was compared to State cancer incidence rates (Koutros et al, 2010), no greater risk of NHL in glyphosate users compared to non-users (De Roos et al, 2005), and NHL risk did not increase with amount of glyphosate use (De Roos et al, 2005).

AHS

AHS began in 1993. It is a collaboration of the US EPA, the National Institute of Environmental Health Sciences (NIEHS), the National Cancer Institute (NCI), and the National Institute for Occupational Safety and Health (NIOSH). The EPA plan to use the results from the AHS in their registration reviews.
<http://www.epa.gov/pesticides/health/ag-health.html>

It is quite surprising that the results of the AHS findings of no excess of NHL as discussed in the De Roos et al., 2005 publication didn't drive a conclusion of no evidence of NHL, particularly since Aaron Blair, the chair of the IARC panel and member of the Epidemiology Workgroup, was one of the Co-Principal Investigators that started the AHS study, is on its Executive Committee and was a co-author with De Roos on the 2005 publication.

From an interview with Arron Blair:

"This is the work Dr. Blair is proudest of after decades of cancer research. This sequence of carefully planned studies eventually led to the extraordinarily productive Agricultural Health Study, which followed more than 89,000 individuals living on farms or applying pesticides commercially in North Carolina and Iowa, and resulted in dozens of articles published in major scientific journals. The great strength of this project is that unlike much other important research on cancer, it does not depend on individuals' ability to recall exposures. It surveys those with a high likelihood of exposure and moves forward through time, asking questions and recording disease as it occurs. This type of experimental design is called a cohort study, and where it is possible, it is able to eliminate many types of bias and confounding factors that plague other experimental designs."

(<https://poisoningourchildren.wordpress.com/2014/03/13/interview-with-aaron-blair-phd-mph->

[scientist-emeritus-at-the-national-cancer-institute-nci/](#)

Again, it is difficult to understand why the findings of the AHS, reported to be the largest, most comprehensive study of agricultural health ever conducted in the United States, were not given sufficient weight to overshadow the weaker case-control studies. This could mean a couple of things: the investigators don't believe the results of their own study that there was no association with NHL, or the study was underpowered to hypothesize findings, which means it was poorly designed to begin with, or it was not performed correctly.

Given that an effect could not be seen in a sample size that large says the biologic effect being proposed is too small to be detected in this study and the findings found in the other smaller studies raise serious questions as to the applicability to a large population and, more important, that there is any cause and effect relationship.

In summarizing AHS publications, Weichenthal et al. (2010,) noted that increased rates in the following cancers were not associated with glyphosate use: overall cancer incidence, lung cancer, pancreatic cancer, colon or rectal cancer, lymphohematopoietic cancers, leukemia, NHL, multiple myeloma, bladder cancer, prostate cancer, melanoma, kidney cancer, childhood cancer, oral cavity cancers, stomach cancer, esophagus cancer and thyroid cancer.

Cohort study

De Roos et al. 2005 – Prospective study of private and commercial applicators in Iowa and North Carolina. Participants completed a 21-page questionnaire.

Among the 54,315 participants, 41,035 (75.5%) had reported using glyphosate and 13,280 (24.5%) had not. Of the 41,035 reported glyphosate users, there 92 cases of NHL or 0.2%. There was no statistically significant association between glyphosate and “all cancers” or any cancer site in analyses of ever versus never-exposed to glyphosate, in analyses of tertiles of cumulative exposure days of glyphosate exposure, or in analyses of tertiles of intensity-weighted exposure days.

Case-control studies

The 3 studies IARC chose as limited evidence were case-control studies. The number of people with NHL that said they had used glyphosate were 36 in De Roos et al. (2003), 51 in McDuffie et al. (2001), and 29 in Eriksson et al. (2008). The AHS study (De Roos et al. 2005) had the largest number with 92.

The studies also used diverse methods to estimate exposure to glyphosate from questionnaires and/or interviews and to classify estimated glyphosate exposure for epidemiologic analyses. The most detailed exposure-response analysis was in the AHS performed by De Roos et al. (2005).

Qualitative review indicated that two (De Roos et al. 2003, Eriksson et al. 2008) studies had RR estimates that rose with increasing exposure. In contrast, the large and important Agricultural Health Study (De Roos et al. 2005) found no evidence of such a trend.

De Roos et al., 2003 -Interviews with subjects or next-of kin to assess pesticide use.

Of 650 people with NHL, 36 said they had used glyphosate (5.5%). Of 1933 people without NHL, 61 said they had used glyphosate (3.2%). The association between glyphosate and NHL was estimated by De Roos et al. (2003) in a standard logistic regression model and in a hierarchical regression model that specified prior distributions for individual pesticides. As described by De Roos et al. (2003), the standard logistic regression model can yield imprecise estimates when modeling multiple pesticides, especially when their use is infrequent and reporting is susceptible to error. To overcome this limitation, they used hierarchical regression models “with the objective of obtaining increased precision and accuracy for the ensemble of estimates.” Moreover, De Roos et al. noted that more conservative prior assumptions specified in the hierarchical models “seemed appropriate in a largely exploratory analysis of multiple exposures for which there is little prior knowledge about how pesticide exposures interact in relation to the risk of NHL.” **A statistically significant association based on a pooled analysis of case-control studies of NHL and glyphosate was reported in a standard logistic regression model, but the pooled odds ratio was not significant in the hierarchical regression.** It is not clear why IARC choose the results of the standard logistic regression model over the hierarchical model that De Roos used to overcome limitations with the other method.

McDuffie et al, 2001 - Mailed, self-reported questionnaire was administered to capture lifetime exposure history and follow up phone call if necessary.

This was a Canadian population-based case-control study of NHL in men. Of 517 men with NHL, 51 said they had used glyphosate or 9.9%. Of 1506 men without NHL, 133 said they had used glyphosate or 8.8%. Glyphosate, which did not show a significant association with NHL in individual chemical analyses, showed odds ratios of 1.0 for use one to two days per year and 2.1 with reported use for three or more days per year. The authors characterized this pattern of ORs as a dose response. However, this characterization was not supported by a trend analysis. Inspection of the data shows only an association in the highest frequency of use category, not a trend of increasing ORs with increasing reported days of use. The study found a slightly elevated OR for any exposure to glyphosate and reported a statistically significant OR of 2.1 for >2 days/year of exposure compared to no exposure, based on 23 cases and 36 controls. The latter OR was **not adjusted for potential confounding by other pesticides**. The results for glyphosate are weak, they lack external support, and they could easily be due to chance, confounding or bias because of the methodologic problems. McDuffie et al. did not consider time since first reported exposure in any of their analyses of glyphosate or other pesticides.

Eriksson 2008 - Self-reported questionnaire determining total work history with detailed questions regarding exposure to pesticides, organic solvents, and other chemicals.

This Swedish case-control study evaluated the association between glyphosate, including duration of exposure (days) and latency (years), and NHL, including histopathologic type. Of 995 people with NHL, 29 (3%) said they used glyphosate; and of the 1016 without NHL, 18 said they had used glyphosate (1.8%). The statistically significant “univariate” association between glyphosate and NHL was attenuated and **no longer significant** after adjustment for age, sex, year of diagnosis or study enrollment, and additional pesticides

Comments on Epidemiology Literature by EU Regulators

JMPR/WHO 2004

“Widely used pesticides, like glyphosate, have recently become a focus of epidemiological research. In the past few years several epidemiological studies have been published that reported weak associations of glyphosate with lymphopoeitic cancers (Nordstrom et al., 1998; Hardell & Erikson, 1999; McDuffie et al., 2001).”

“ However, the results of these studies do not meet generally accepted criteria from the epidemiology literature for determining causal relationships. Generally, the associations were rather weak and rarely statistically significant. Control for potential confounding factors, including other pesticides, was not possible owing to limited available information and small numbers of subjects. It was not measured whether there actually was any internal exposure or the extent of such exposure and, accordingly, a possible dose–response relationship could not be evaluated.”

BfR 2015

In epidemiological studies in humans, there was no evidence of carcinogenicity and there were no effects on fertility, reproduction and development or of neurotoxicity that might be attributed to glyphosate.

They looked at all the case-control studies including De Roos 2003, McDuffie 2001 and Eriksson 2008, as well as De Roos 2005.

References

Laura Freeman, Co-Principal Investigator of the AHS and with the Division of Cancer Epidemiology and Genetics, National Cancer Institute, was a member of the President’s Cancer Panel on October 21, 2008. In her 2009 follow up publication she reported on the AHS findings to date where no cancer sites were associated with glyphosate (the reference in her publication was De Roos et al, 2005).

Freeman, L. B. 2009. Evaluation of Agricultural Exposures: The Agricultural Health Study and the Agricultural Cohort Consortium. President's Cancer Panel - October 21, 2008. *Reviews on Environmental Health* 24 (4):311-318.

<http://deainfo.nci.nih.gov/advisory/pcp/pcp1008/summary.pdf>